Remarks

Claims 1-23 are pending in this application. In the Office Action, the Examiner has required election to one of the following inventions: Group I, claims 1-22, drawn to methods of determining haplotype structures; or Group II, claim 23, drawn to a kit for determining haplotypes.

In a telephone conversation with the Examiner on November 18, 2005, the Applicant's representative, Sarah Eurek, made a provisional election of Group I, claims 1-22. Applicant hereby affirms the election of Group I without traverse. Accordingly, claim 23 is hereby canceled.

Claims 1-22 have been rejected. By this amendment, claims 1-17 and 23 have been cancelled, without prejudice or disclaimer, claim 18 has been amended, and new claims 24 -36 have been added. The amendments and new claim do not constitute new matter. In view of the above-described amendments and following remarks, reconsideration of claims 18-22, and consideration of new claims 24-36 is respectfully requested.

Claim Rejections - 35 U.S.C. § 112

The Examiner has rejected claims 3, 4, 5, 12, and 17 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention.

Claims 3, 4, 5, 12 and 17 have been canceled, thereby rendering the rejection moot.

Claim Rejections - 35 U.S.C. § 102

Claims 1, 2, 13, 14 and 16 are rejected under 35 U.S.C. § 102(b) as being anticipated by Fanning, et al. (1997), *Tissue Antigens*, vol. 50, pages 23-31, 07/1997 (hereinafter referred to as "Fanning"). (Note: For purposes of this rejection, the Examiner has interpreted the enriched nucleic acid fraction of claim 1 to have *outside* the range of 2 to 30 times more of one allelic variant of the nucleic acid than the other allelic variant of the nucleic acid).

Claims 1, 2, 13, 14 and 16 have been cancelled, thereby rendering their rejection moot. Applicant submits that the new claims are not anticipated by Fanning.

The Examiner has stated that Fanning teaches "obtaining an enriched nucleic acid fraction of a haplotype of 3 SNPs that is present at a higher level than the corresponding different haplotype of the same SNP sites by *allele-specific PCR*" (emphasis added). Applicant notes that the method taught by Fanning differs greatly from the method of the present invention. Fanning clearly states on Page 23, 2nd column, first paragraph, that "the advantage of this (Fanning) strategy is that polymorphisms are physically linked through *PCR* and haplotypes can be determined..." (emphasis added). The method described in Fanning is necessarily limited to haplotyping polymorphisms that are close enough to actually be linked by PCR.

In contrast to Fanning, the method of the instant invention is not limited by any constraints on distance between SNP sites. That is, the SNP sites that are haplotyped according to Applicant's invention do not necessarily have to be close enough to be linked by PCR, although they may be. As recited in claims 24-36 that have been added by this amendment, the first allele of the first selected SNP site is specifically hybridized with an allele specific hybridization probe to provide an enriched nucleic acid sample, then the allele of another SNP site that is also located on one of the variant alleles of the nucleic acid is determined, for example by using PCR to amplify the second SNP site using primers that need flank only that particular SNP site, although they may flank both SNP sites.

While Fanning teaches obtaining an enriched nucleic acid fraction via allele-specific PCR, nowhere does Fanning teach or suggest using a hybridization probe that is specific for a particular allele of a first SNP site. And nowhere does Fanning teach or suggest isolating allelic variants that bind to such a hybridization probe to provide a nucleic acid fraction that is enriched for allelic variants having a particular allele of a first SNP site. And nowhere does Fanning teach or suggest determining the identity of the alleles for at least a second SNP site on the nucleic acid and determining the relative amounts in the nucleic acid fraction of each of the allelic variants that contain the identified alleles. Lacking any such disclosure, Fanning simply does not anticipate Applicant's invention, as recited in new claims 24-36. Applicant submits that the clams, as amended, are allowable.

Claims 1-5, 7, and 12-17 are rejected under 35 U.S.C. §102 (e) as being anticipated by Landers, U.S. Patent No. 6,844,154 (hereinafter referred to as "Landers"). (Note: For purposes of

this rejection, the Examiner has interpreted the enriched nucleic acid fraction of claim 1 to have *outside* the range of 2 to 30 times more of one allelic variant of the nucleic acid than the other allelic variant of the nucleic acid).

Claims 1-5, 7, and 12-17 have been cancelled, thereby rendering their rejection moot. Applicant submits that the new claims are not anticipated by Landers.

The Examiner has stated that Landers teaches "obtaining an enriched nucleic acid fraction that contains more of one allelic variant of a haplotype of two SNPs by hybridization to a probe on a *solid support* that is specific for one particular allele of one SNP of a haplotype" (emphasis added). The method of Landers, like that of Fanning, is quite different from the method of the current invention. Landers teaches a method wherein the nucleic acid is bound to a solid support surface, then subjected to PCR amplification of both polymorphic loci (as shown in Figure 1, and all 3 examples given) before allele-specific hybridization occurs (see Landers at col. 14, lines 42-54). Amplification of the 2 polymorphic loci gives rise to the same limitations as were described for Fanning above, most importantly necessitating that the loci be relatively close in position. In sharp contrast to Landers, the instant invention does not require amplification of all of the polymorphic loci on the nucleic acid that is being haplotyped. Because each SNP site may be separately amplified, importantly without the need to use primer sets that flank ALL SNP sites, the method according to the instant claims does not constrain the distance between the polymorphic loci that are to be haplotyped.

Landers does not teach or suggest using a hybridization probe that is specific for a particular allele of a first SNP site and first isolating allelic variants that bind to such a hybridization probe to provide a nucleic acid fraction that is enriched for allelic variants having a particular allele of a first SNP site. In addition, Landers does not teach or suggest determining the identity of the alleles for at least a second SNP site on the nucleic acid and determining the relative amounts in the nucleic acid fraction of each of the allelic variants that contain the identified alleles. Lacking any such disclosure, Landers simply does not anticipate Applicant's invention, as recited in new claims 24-36. Applicant submits that the clams, as amended, are allowable.

Claim Rejections - 35 U.S.C. § 103

Claims 1, 2, 6, 13, 14 and 16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Fanning. (Note: For purposes of this rejection, the Examiner has interpreted the enriched nucleic acid fraction of claim 1 to have *outside* the range of 2 to 30 times more of one allelic variant of the nucleic acid than the other allelic variant of the nucleic acid).

Claims 1, 2, 6, 13, 14 and 16 have been cancelled, thereby rendering their rejection moot. Applicant submits that the new claims are not rendered obvious by Fanning.

In rejecting claims 1, 2, 6, 13, 14, and 16, the Examiner stated that "the ordinary artisan would have been motivated to improve the method of haplotype analysis taught by Fanning through routine experimentation to provide optimum or workable ranges."

Applicant respectfully disagrees with the Examiner. Fanning provides no motivation whatsoever to adapt the methods described therein to provide for isolation of allelic variants based on the specific sequence of an allele of one SNP site, and thereafter separately determine the identity of alleles and relative amounts of a second SNP site so as to arrive at the haplotype for the nucleic acid in a subject. At most, Fanning teaches the use of PCR primer sets to identify the alleles of SNPs in a single reaction. Fanning makes no mention or suggestion of the desirability of first enriching based on the specific sequence of a particular allele of one selected SNP site. And Fanning makes no mention or suggestion of the desirability of using primer sets that flank only one SNP. The Examiner has provided no evidence as to how "routine experimentation to provide optimum or workable ranges" would lead to such significant radical changes as would be needed to modify the method described in Fanning to arrive at the method of Applicant. Applicant submits that one of ordinary skill in the art could not simply adapt the method of Fanning to arrive at the claimed invention. Accordingly, Applicant submits that the new claims are not rendered obvious under 35 U.S.C. § 103(a) in light of Fanning.

Claims 1-7 and 12-17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Landers. (Note: For purposes of this rejection, the Examiner has interpreted the enriched nucleic acid fraction of claim 1 to have *outside* the range of 2 to 30 times more of one allelic variant of the nucleic acid than the other allelic variant of the nucleic acid).

Claims 1-7 and 12-17 have been cancelled, thereby rendering their rejection moot. Applicant submits that the new claims are not rendered obvious by Landers.

In rejecting claims 1-7 and 12-17, the Examiner stated that "the ordinary artisan would have been motivated to improve the method of haplotype analysis taught by Landers through routine experimentation to provide optimum or workable ranges."

Applicant respectfully disagrees with the Examiner. As with Fanning, Landers provides no motivation whatsoever to adapt the methods described therein to provide for isolation of allelic variants based on the specific sequence of an allele of one SNP site, and thereafter separately determine the identity of alleles and relative amounts of a second SNP site so as to arrive at the haplotype for the nucleic acid in a subject. At most, Landers teaches the binding of a nucleic acid to a solid support, then PCR amplification of both the 2 polymorphic loci to be haplotyped, followed by allele-specific hybridization. Like Fanning, Landers makes no mention or suggestion of the desirability of first enriching based on the specific sequence of a particular allele of one selected SNP site. And like Fanning, Landers makes no mention or suggestion of the desirability of using primer sets that flank only one SNP. The Examiner has provided no evidence as to how "routine experimentation to provide optimum or workable ranges" would lead to such significant radical changes as would be needed to modify the method described in Landers to arrive at the method of Applicant. Applicant submits that one of ordinary skill in the art could not simply adapt the method of Landers to arrive at the claimed invention. Accordingly, for these reasons, and in view of other differences between the cited references and the instant claims, Applicant submits that the new claims are not rendered obvious under 35 U.S.C. § 103(a) in light of Landers.

Claims 8-11 and 18-22 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Landers as applied to claims 1-7 and 12-17 above, and further in view of Sorenson, U.S. Patent No. 6,020,124 (hereinafter referred to as "Sorenson"). (Note: For purposes of this rejection, the Examiner has interpreted the enriched nucleic acid fraction of claim 8 to have *within* the range of 2 to 30 times more of one allelic variant of the nucleic acid than the other allelic variant of the nucleic acid).

Claims 8-11 have been cancelled, thereby rendering their rejection moot. Applicant submits that claims 18-22 and the new claims are not rendered obvious by Landers in view of Sorenson.

The Examiner has pointed out that Landers does not teach a method of haplotyping which involves amplifying the nucleic acids in the enriched nucleic acid fraction prior to identifying the alleles of interest. However, the Examiner has stated that Sorenson teaches that the nucleic acid sample can be amplified by PCR prior to determining the alleles present in a particular nucleic acid. The Examiner stated that "it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of haplotype identification taught by Landers to include PCR amplification of the nucleic acids in the enriched nucleic acid fraction prior to identifying the alleles of interest . . . in view of the teachings of Sorenson."

However, it should be noted that Sorenson, like Fanning, teaches a method of performing allele-specific PCR as opposed to allele-specific hybridization, which is the method employed in the instant invention. Again, Applicant would like to point out that the instant invention does not require amplification of the loci to be haplotyped, in fact, amplification of the loci necessarily would require that the SNP sites be in close proximity to one another for purposes of haplotyping. The instant invention is not limited by the distance between the SNP sites to be haplotyped because there is no need to amplify the nucleic acid the SNP sites are located on, unlike Sorenson, Fanning, and Landers. The enrichment process of the instant invention is not equivalent to the amplification processes described in Fanning, Landers, or Sorenson because amplification means generating more of the target molecules, whereas in the instant invention only enrichment, which is selectively increasing the ratio of enriched molecules to non-enriched molecules, is needed for accurate haplotyping of SNP sites that are any distance apart on the same nucleic acid molecule. Neither Landers nor Sorensen makes any mention or suggestion of the desirability of first enriching based on the specific sequence of a particular allele of one selected SNP site. And neither Landers not Sorensen makes any mention or suggestion of the desirability of using primer sets that can flank only one SNP. Applicant submits that neither reference provides any motivation to modify or any teaching or suggestion as to how one of ordinary skill in the art could adapt the described method to arrive at the claimed invention. Accordingly, for these reasons, and in view of other differences between the cited references and the instant claims, Applicant submits that the new claims are not rendered obvious under 35 U.S.C. § 103(a) in light of Landers.

Applicant respectfully submits that claims 18-22, and new claims 24-36 are in condition for allowance. Prompt notice of such allowance is respectfully requested.

This response is being filed with a request for an extension of time of three months and authorization to the Office to charge the required fee for a small entity to Deposit Account No. 03-0172.

Respectfully submitted,

Date: June 19, 2006

By: /diane h. dobrea/
Diane Dobrea
Reg. No. 48,578
(614) 621-7788